November 6, 2003

MEMORANDUM

Subject: Transmission of Background Materials for the Session of the December 9-10, 2003 FIFRA Scientific Advisory Panel Entitled "Proposed Science Policy: PPARα Agonist-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments"

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Attached is the document "Proposed OPPTS Science Policy: PPARα Agonist-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments." The purpose of this guidance document is to describe the approach that OPPTS is proposing to evaluate the scientific information regarding the mode of action (MOA) of PPARα agonists in rodent hepatocarcinogenesis, the data necessary to establish the MOA for PPARα agonist-induced rodent liver tumors and the relevance of this hepatic MOA in humans including children. The Office of Prevention, Pesticides and Toxic (OPPTS) is requesting that the FIFRA Scientific Advisory Panel comment on the soundness of this proposed science policy (see Charge below).

Developments in the area of research on peroxisome proliferating chemicals have led to a reevaluation of the state of the science to characterize the mode(s) of action (*i.e.,* PPARα agonism) and the human relevance of rodent tumors induced by PPARα agonists. Recently, the ILSI Risk Science Institute (ILSI RSI) convened a large expert technical group (ILSI document, 2003) to evaluate new information on the association between PPARα agonism and the induction of tumors by peroxisome proliferating chemicals. OPPTS considered the 2003 ILSI report as well as the pertinent scientific literature in developing its proposed science policy.

Attachments:

Document For Review With Respect to Charge–

- ❑ OPPTS October 2003 Draft Document Proposed Science Policy: PPARα Agonist-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments. (Enclosed)

Background Material–

- ❑ ILSI RSI 2003 PPARα Agonist-Induced Rodent Tumors: Mode(s) of action and Human Relevance. (Will be forwarded separately)

Charge to the Panel:

Please provide comment and advice on the following questions. In addressing these questions consider the completeness of the data sets evaluated.

Issue 1: Rodent PPAR α Mode of Action for Hepatocarcinogenesis

OPPTS has concluded that there is sufficient weight of evidence to establish the mode of action for PPARα agonist-induced rodent hepatocarcinogenesis. It is proposed in the OPPTS document that PPARα agonists activate PPARα leading to an increase in cell proliferation and a decrease in apoptosis, and eventually further clonal expansion of preneoplastic cells and formation of liver tumors. The key events in PPARα agonist-induced hepatocarcinogenesis may be classified as either causal (required for this MOA) or associative (marker of PPARα agonism).

> **Question 1** - Please comment on the weight of evidence and key events for the proposed mode of action for the PPARα agonist-induced rodent hepatocarcinogenesis. Please comment on the adequacy of the data available to identify the key events in the PPARα MOA. Discuss whether the uncertainties and limitations of these data been adequately characterized.

Issue 2: Relative Sensitivity of Fetal, Neonatal, and Adult Rodent

OPPTS has provided a review of the ontogeny of PPARα expression and peroxisomal assemblage during fetal and postnatal development in rodents as well as an analysis of the available data evaluating effects on peroxisomal proliferation, peroixsomal enzyme activity, and liver weights following exposure to PPARα agonists during fetal and postnatal development in rats and mice (see Section V of the OPPTS Document). Based on this analysis, OPPTS concluded that fetal and neonatal rats do not exhibit an increased sensitivity to PPARα agonist-induced hepatocarcinogenicity relative to the adult rodent. Therefore, any conclusions regarding this mode of action in adult rodents would also apply to young rodents, and similarly any conclusions regarding the relevance of this mode of action for human hepatocarcinogenesis would apply to the young, as well as the adults.

Question 2 - Please comment on the weight of the evidence approach and mechanistic data used to support this conclusion.

Issue 3: Human Relevance

OPPTS has provided an analysis of a variety of *in vitro* and *in vivo* studies on the key events pertaining to PPARα agonist-induced hepatocarcinogensis with hamsters, guinea pigs, non-human primates, and humans. Based on the weight of the evidence, OPPTS concludes that although PPARα agonists can induce liver tumors in rodents and while PPARα is functional in humans, quantitatively, humans and nonhuman primates are refractory to the hepatic effects of PPARα agonists.

Therefore, OPPTS is proposing the following scientific policy:

> When liver tumors are observed in long term studies in rats and mice, and 1) the data are sufficient to establish that the liver tumors are a result of a PPARα agonist MOA and 2) other potential MOAs have been evaluated and found not operative, the evidence of liver tumor formation in rodents should not be used to characterize potential human hazard.

Question 3 - Please comment on the data and weight of evidence regarding the hepatic effects of PPARα agonists in humans, and please comment on the proposed OPPTS's science policy regarding human relevance.

Issue 4: Data Requirements

OPPTS has proposed a data set that would be sufficient to demonstrate that PPARα agonism is the mode of action for the induction of rodent liver tumors. The data set includes evidence of PPARα agonism (*i.e.* from an *in vitro* reporter gene assay), *in vivo* evidence of an increase in number and size of peroxisomes, increases in the activity of acyl CoA oxidase, and hepatic cell proliferation. The *in vivo* evidence should be collected from studies designed to provide the data needed to show dose-response and temporal concordance between precursor events and liver tumor formation.

> **Question 4** - Please comment in general on the proposed data set and particularly on its adequacy to demonstrate that a PPARα agonist-mediated MOA is operating in rodent hepatocarcinogenesis.

Issue 5: Other Tumors Induced by PPARα Agonists

Some PPARα agonists may also induce pancreatic acinar cell and Leydig cell tumors in rats and modes of action involving agonism of PPARα have been proposed. An in depth analysis of these tumors is provided in the 2003 ILSI technical panel report. Based on this analysis, OPPTS agrees that the data available to date are insufficient to support the proposed MOAs.

Thus, OPPTS is proposing the following science policy:

> Given the limited evidence available to support that a chemical may induce pancreatic and Leydig cell tumors through a PPARα agonist mode of action, the evidence is inadequate at this time to support a linkage between PPARα agonism and formation of these tumor types. Thus, it is presumed that chemicals that induce pancreatic or Leydig cell tumors may pose a carcinogenic hazard for humans.

> **Question 5** - Please comment on OPPTS's conclusion that there is limited evidence that a chemical may induce pancreatic and Leydig cell tumors through a PPARα agonist mode of action, and OPPTS's proposed science policy regarding other tumors induced by PPARα agonists.